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Review Article

A systematic review and meta-analysis on the influence of biological implant surface coatings on periimplant bone formation

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Key Words: animal experiments, bone implant interactions, dental implant, histomorphometry, surface coatings complexes

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INTRODUCTION

The application of dental implants for the replacement of missing teeth increased strongly throughout the last 30 years. Innovations in implant material, design, and surface structure improved implant stability and shortened healing periods.[1,2] Following implant placement, especially the initial interaction with proteins and cells is influenced by the implant surface.[3,4] Most implant surface treatments aim at enhancing the activity of bone-forming cells and their mediators to increase new bone formation and promote earlier osseointegration and higher secondary implant stability. Microstructured implant surfaces showed advantageous characteristics for bone formation and are the current standard of surface treatment.[5] Besides microtopography, other biophysical factors such as surface chemistry, surface charge, and wettability also have an influence on bone formation.[6]

Yet another surface modification to further stimulate osseointegration is the coating of implant surfaces with biological components.[7–9] For bone, these may be organic as well as inorganic in nature, and both can potentially influence cellular activity during periimplant healing. In this context, many different types of surface coatings have been analyzed in recent years. These include coatings with extracellular matrix (ECM) proteins, peptides, growth factors, calcium phosphate phases, lipids, and so on. In animal studies, the application of high dosages of the growth factor BMP-2[10] as well as other approaches using ECM components like collagen and glycosminoglycans[9,11] or peptides derived from ECM proteins like RGD peptide[12] have been reported to show an effect on bone healing.

While these physiological approaches for enhancing bone healing hold great appeal as the next generation of surface modifications and while numerous studies have

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TABLE I. Electronical Search Protocol

#	Searches	Results
1	Dental implants/	13,133
2	(dental adj3 implant*).ti,ab.	8848
3	exp dental implantation, endosseous/	12,976
4	exp denture design/or dental prothesis design.mp.	13,207
5	1 or 2 or 3 or 4	34,175
6	"Prostheses and implants"/or prosthesis design/	67,367
7	Implants, experimental/	2417
8	(implant or implants).tw.	105,299
9	6 or 7 or 8	156,751
10	(dental or dentistry).ab,jn,kw,ti,sb.	180,020
11	9 and 10	11,762
12	5 or 11	35,960
13	Coated materials, biocompatible/	9633
14	((surfac* or implant*) adj3 (coated or coating or lining or covering or covered or plating or finishing or loaded or loading or sputter*)).tw.	19,184
15	((pulse* or spray* or beam or assisted) adj5 deposit*).tw.	2372
16	exp Biomimetics/	2916
17	biomimetic*.tw.	5921
18	exp body fluids/	275,882
19	(body adj3 fluid*).tw.	15,643
20	simulated.tw.	84,250
21	(18 or 19) and 20	2729
22	exp collagen/or collagen.mp.	163,682
23	exp "Intercellular signaling peptides and proteins"/	756,751
24	((growth or signaling or intercellular) adj3 (factor* or protein* or peptide*)).tw.	294,412
25	(surface or coated or coating or lining or covering or covered or plating or finishing or loaded or loading or sputter*).tw.	959,310
26	(22 or 23 or 24) and 25	82,808
27	13 or 14 or 15 or 16 or 17 or 21 or 26	118,482
28	12 and 27	3322
29	Animals/not exp rodentia/	2,617,285
30	(dog* or canine or hound* or hog* or swine* or pig* or porcine or cat* or feline or goat* or caprine or sheep* or ovine).tw.	1,794,683
31	29 or 30	3,810,566
32	28 and 31	970

been conducted to assess their efficiency, there is still little systematic evidence of their effects.

The aim of this systematic review and consecutive meta-analysis was to systematically analyze large animal studies conducted between 2003 and 2013, which investigated bone formation around biological implant surface coatings. It was analyzed whether coated surfaces show an enhanced periimplant bone formation in comparison to uncoated titanium surfaces. Furthermore, the degree of enhancement as measured by the bone implant contact (BIC) was evaluated in relation to animal-specific factors of influence.

MATERIALS AND METODS

Eligibility criteria

The following inclusion criteria were defined: publication period between January 01, 2003, and December 31, 2013, English language, large animal studies with a minimum of six animals/study, and comparison of biological implant surface coatings to uncoated titanium. Both studies in unimpaired (healthy) bone and in locally or systemically impaired animal models were considered. Only studies meeting all the inclusion criteriae were included in the review.

The following exclusion criteria were defined: human, rodent, and rabbit studies. Studies analyzing only inorganic surface coatings were excluded, while studies analyzing biological surface coatings together with inorganic surfaces were included.

Information sources

A data search in the databases Medline (OvidSP), Biosis, and Scopus were performed for large animal studies. The search was limited to the English language and aimed at studies comparing periimplant bone formation of uncoated titanium implants to implants coated with biological components. The term large animal was defined as follows: pig (including minipig), dog, sheep, goat, and monkey. It did not include rodents. The literature search-process was carried out by an information specialist officer (MG) of the main library of the University of Zurich.

Search

The detailed search terms and the search history protocol are shown in Table I. The retrieved studies underwent a deduplication program.

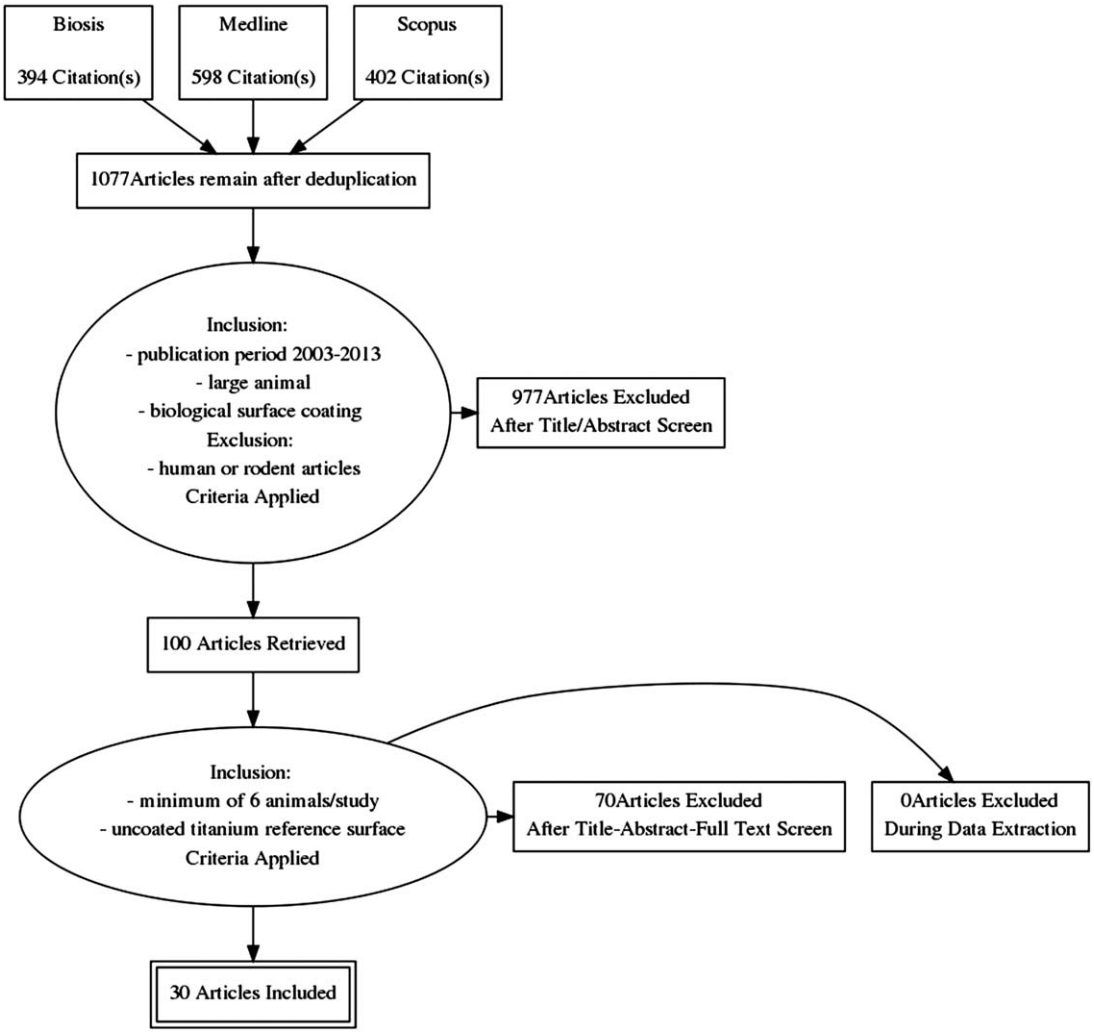

FIGURE 1. PRISMA diagram.

Study selection

Two investigators (GJ and JJ) each screened half of the titles and abstracts of all studies for meeting the inclusion or exclusion criteriae in a first round. Disagreement was solved by discussion between the investigators GJ, JJ, and BS. Full texts were obtained in cases where titles and abstracts did not provide sufficient information regarding the inclusion/exclusion criteria. In a second round, two investigators (GJ and JJ) each screened half of the remaining studies as full texts for meeting the inclusion criteria. Disagreement was solved by discussion between the investigators GJ, JJ, and BS. Kappa and McNemar test served for the evaluation of intraexaminer and interexaminer agreement (Fig. 1).

Data collection process and meta-analysis

Full texts of all included studies were analyzed, and data were extracted and coded in an excel table. Following data extraction, parameters of analysis were identified which enabled a comparison of the study results by means of a meta-analysis. To gain a better understanding of a potential effect of biological surface coatings on periimplant bone formation, a meta-analysis of those studies that measured the effect on the BIC was performed. This served to quantify possible effects of surface coatings on bone formation. The meta-analysis was based solely on studies in unimpaired bone using the analyzed test and control implants that measured BIC and standard deviation (SD). If BIC was not reported, the study was excluded from the meta-analysis. If SD was not reported and minimum (min)/maximum (max) or the 95% confidence interval (95% CI) was available, SD was computed based on these parameters by the statistian (MR). If BIC/SD were only extractable from a graph, the absolute values were measured from the graph. The meta-analysis evaluates the difference in BIC between test and control surfaces with regard to the type of surface coating, animal species, and implant localization.

Data items

All included studies were analyzed with respect to the following parameters: animal species, systemically impaired/unimpaired animal model, locally compromised/uncompromised bone, animal number, total implant number, implant

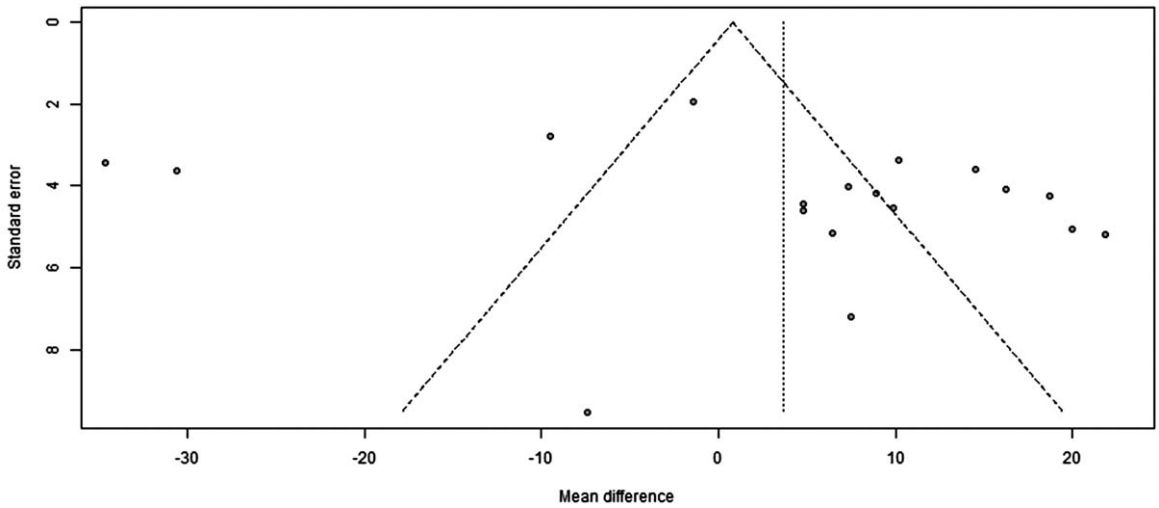

FIGURE 2. Funnel plot of the results showing the standard error versus the mean difference of the studies. Studies with a negative mean difference and large standard errors seem to be underrepresentated in our analysis, which could be an indicator of a publication bias.

localization, healing mode, loaded or nonloaded, time points of examination, number of different surfaces, type of biological surface coating, type of titanium reference surface, method of implant analysis, and BIC.

Risk of bias

A Funnel plot was produced to estimate the publication bias of the studies in the meta-analysis (Fig. 2).

Summary measures and synthesis of results

Mean and 95% CI of BIC were calculated and included in the meta-analysis. The parameters effect size and relative effect were also calculated. Effect size is the absolute BIC change measured and calculated as the mean difference between BIC percentage of test and reference surface. The relative effect is the percentage of the absolute BIC change (effect size) in relation to the BIC of the reference surface and is calculated as the following equations:

$$\mathrm{BIC}_{\mathrm{effect\ \ size}}\,(\%)/\mathrm{BIC}_{\mathrm{test\ \ surface}}\,(\%)$$

Effect size of each study, as well as the summary effect size and summary relative effect are shown in the column mean difference in Figure 3. The mean effect size values were pooled using random-effect models to calculate a summary effect size and corresponding two-sided 95% CI. The DerSimonian and Laird method was used to estimate the between studies variance τ^2. The I^2 statistic was also calculated to estimate the heterogeneity between studies. The weights per study can be found in column W (random) in Figure 3. As a result, the summary effect size is the effect size measured over all studies included in the meta-analysis. The summary relative effect was calculated as the absolute value of the summary effect size divided by the weighted mean of the reference BIC percentage. Results were considered statistically significant if p values were <0.05. The primary analysis used data from all studies with all test surfaces and both blasted/etched and polished/machined reference surfaces. All analyses are exploratory in nature, as no correction for multiple testing was applied. All statistical meta-analyses were performed using R v3.1.0 and the R-package "meta" v4.2-0. The above-described analyses were calculated by the statistian (MB).

Additional analyses

For descriptive results, the statistical analysis was performed using SPSS (Version 22; IBM, New York). Absolute and relative frequencies of discrete variables were computed. In addition, the 95% CI for the true proportion was computed according to Wilsons procedure. For continuous variables, means and SDs were computed. Intra- and interexaminer agreements were investigated by the kappa measure.[13,14] In addition, the McNemar test was applied to evaluate a possible disagreement between the examiners. Additional analyses were calculated by the statistian (MR).

RESULTS

Study selection

The literature search revealed a total number of 1394 titles, of which 1077 titles remained after automatic deduplication. In the first round of screening process, 977 articles were excluded. Of the remaining 100 studies, a further 70 studies were excluded in a second round of screening. The final 30 studies were included in this systematic review. An overview on all included studies is given in Table II. Figure 1 shows the search pathway. Main reasons for exclusion were the application of rodent or rabbit models, lack of a biologically modified test surface or lack of an uncoated titanium reference surface, pilot studies with less than six animals, human studies, and entirely different experimental setup, for example, *in vitro* studies.

Study characteristics and descriptive results

Experimental details of the 30 studies include animal parameters (total number, species, and health condition systemic/local), implant parameters (total number, material,

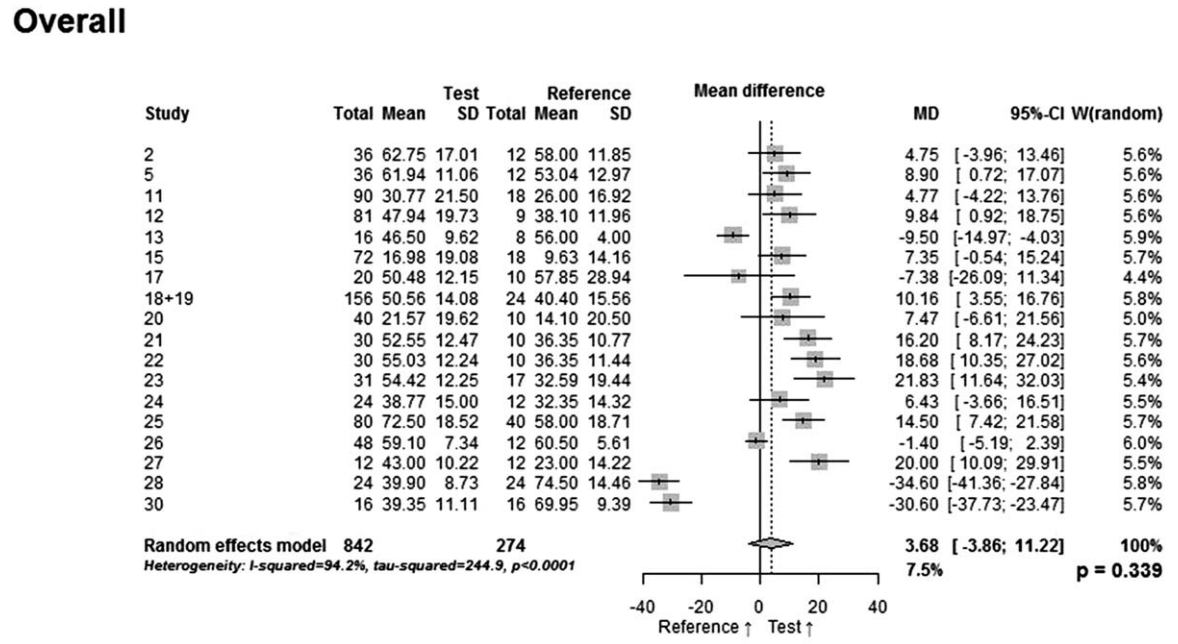

FIGURE 3. Overall results of the meta-analysis of all test surfaces compared to all reference surfaces. The mean difference (MD) calculated with the mean BIC (mean) and standard deviation (SD) of test and reference surfaces shows a summary effect size of 3.68 pp more BIC and a summary relative effect of 7.5 pp. The summary effect size was calculated using a random effect model, and the weight per study can be found in column W (random).

design, length, diameter, localization, healing mode, and loading), analysis (time points and method), and implant surface parameters (number of tested surfaces per study, type of reference surface, type of test surface, and coating components).

Animal parameters. The total animal number per study differed and varied between 6 and 20 (mean 13) animals. The 30 studies used five different animal species, which in all cases were unimpaired and systemically healthy. Dog (16) and pig (9) animal models were most common, and smaller groups include goat and sheep as well as one monkey model. Six studies used local defect models. In five studies, implants were partly placed supracrestally,[15–19] in one a periimplant gap model[11] was created. The remaining 24 studies applied no defect models.

Implant parameters. The applied number of implants per study showed a range from 24 to 110 implants. The mean implant number per study was 60. The implant material in all 30 studies was titanium, two studies further investigated zirconia implants.[6,20] Screw-shaped implants were used in 27 studies, three studies applied experimental implant designs.[12,21,22] The mean implant length was 9 mm. The mean implant diameter reported in 29 studies was about 4 mm, two studies reported an inner implant diameter of 2.7 mm.[23,24] In 23 studies, implants were placed intraorally, in seven studies extraorally. In general, most implants were placed into the mandible: In the intraoral studies, implants in five studies were placed in the upper jaw and implants in 18 studies in the lower jaw. Within the seven extraoral studies, in two studies, implants were placed in pelvic bone, three in skull bone and two in femoral bone. In 29 studies implants healed submerged (covered by the gingiva), in one study nonsubmerged. Implants of all 30 studies were unloaded.

Analysis parameters. All 30 studies used 1, 2, or 3 time points of analysis (T1, T2, and T3). Implant follow-up time was up to 168 days. Mean T1 examination time point was 36 days. In 21 studies, a second time point (T2) was analyzed (mean T2 time point 52 days). In eight studies, a third examination time point (T3) was analyzed (mean T3 time point 40 days).

The most common method of analysis for the investigation of surface effects was qualitative histology and quantitative histomorphometry: BIC and bone volume (BV). Other methods of analysis were immunohistochemistry, fluorochrome labeling, mechanical testing (removal torque test), and radiography. Twenty-six studies performed histological analyses, nine studies performed fluorochrome labeling, one study used immunohistochemistry, four studies applied mechanical testing, and 11 studies used radiographic methods.

Implant surface parameters. Ten different biological surface components could be identified. The authors allocated these 10 components to the following four groups: (1) inorganic components, (2) growth factors, (3) peptides, and (4) ECM components. Details about test and reference surfaces of all 30 studies are shown in Table III.

TABLE II. List of All 30 Studies Included in the Systematic Review

Nr	Author	Year	Title
1	Alghamdi et al.	2013	Biological response to titanium implants coated with nanocrystals calcium phosphate or type 1 collagen in a dog model
2	Barros et al.	2009	Effect of biofunctionalized implant surface on osseointegration: a histomorphometric study in dogs
3	de Barros et al.	2013	Bone formation in a local defect around dental implants coated with extracellular matrix components
4	Ferguson et al.	2008	Biomechanical comparison of different surface modifications for dental implants
5	Germanier et al.	2006	Enhanced bone apposition around biofunctionalized sandblasted and acid-etched titanium implant surfaces. A histomorphometric study in miniature pigs
6	Huh et al.	2012	Effects of anodized implants coated with *Escherichia coli*-derived rhBMP-2 in beagle dogs
7	Huh et al.	2011	Alveolar ridge augmentation using anodized implants coated with *Escherichia coli*-derived recombinant human bone morphogenetic protein2
8	Hunziker et al.	2012	Osseointegration: the slow delivery of BMP-2 enhances osteoinductivity
9	Langhoff et al.	2008	Comparison of chemically and pharmaceutically modified titanium and zirconia implant surfaces in dentistry: a study in sheep
10	Leknes et al.	2013	Alveolar ridge augmentation using implants coated with recombinant human growth/differentiation factor-5 (rhGDF-5): radiographic observations
11	Liu et al.	2007	The influence of BMP-2 and its mode of delivery on the osteoconductivity of implant surfaces during the early phase of osseointegration
12	Mueller et al.	2011	Comparative analysis of osseointegration of titanium implants with acid-etched surfaces and different biomolecular coatings
13	Nikolidakis et al.	2009	The effect of a low dose of transforming growth factor beta1 (TGF-beta1) on the early bone-healing around oral implants inserted in trabecular bone
14	Polimeni et al.	2010	Alveolar ridge augmentation using implants coated with recombinant human growth/differentiation factor-5: histologic observations
15	Ramazanoglu et al.	2011	The effect of combined delivery of recombinant human bone morphogenetic protein-2 and recombinant human vascular endothelial growth factor 165 from biomimetic calcium-phosphate-coated implants on osseointegration
16	Ramazanoglu et al.	2013	Bone response to biomimetic implants delivering BMP-2 and VEGF: An immunohistochemical study
17	Schliephake et al.	2005	Effect of immobilized bone morphogenic protein 2 coating of titanium implants on peri-implant bone formation
18	Schliephake et al.	2009	Effect of modifications of dual acid-etched implant surfaces on peri-implant bone formation. Part I: organic coatings
19	Schliephake et al.	2009	Effect of modifications of dual acid-etched implant surfaces on peri-implant bone formation. Part II: calcium phosphate coatings
20	Schliephake et al.	2003	Biological performance of biomimetic calcium phosphate coating of titanium implants in the dog mandible
21	Schliephake et al.	2005	Functionalization of dental implant surfaces using adhesion molecules
22	Schliephake et al.	2006	Biomimetic calcium phosphate composite coating of dental implants
23	Schouten et al.	2009	Effects of implant geometry, surface properties, and TGF-beta1 on peri-implant bone response: an experimental study in goats
24	Schulz et al.	2014	Coating with artificial matrices from collagen and sulfated hyaluronan influences the osseointegration of dental implants
25	Stadlinger et al.	2009	Increased bone formation around coated implants
26	Stadlinger et al.	2008	Suitability of differently designed matrix-based implant surface coatings: an animal study on bone formation
27	Sverzut et al.	2012	Effects of type I collagen coating on titanium osseointegration: histomorphometric, cellular and molecular analyses
28	Wikesjö et al.	2008	Bone formation at recombinant human bone morphogenetic protein-2-coated titanium implants in the posterior maxilla (type IV bone) in non-human primates
29	Wikesjö et al.	2008	Alveolar ridge augmentation using implants coated with recombinant human bone morphogenetic protein-2: histologic observations
30	Wikesjö et al.	2008	Bone formation at recombinant human bone morphogenetic protein-2-coated titanium implants in the posterior mandible (type II bone) in dogs

TABLE III. Distribution of Surface Coatings

Study	R	I	GF	P	ECM
1. Alghamdi et al.[21]	X (*)	X (**)			X (*)
2. Barros et al.[29]	X (*)	X (*)		X (*)	
3. de Barros et al.[11]	X (***)				X (**/****)
4. Ferguson et al.[20]	X (*/***)	X (*/***)			X (*/****)
5. Germanier et al. (2006)	X (*)			X (**)	
6. Huh et al.[15]	X (***)		X (*)		
7. Huh et al.[14]	X (***)		X (*)		
8. Hunziker et al.[25]	X (*)	X (**)	X (*)		
9. Langhoff et al.[6]	X (*)	X (*/***)			X (*/****)
10. Leknes et al.[17]	X (***)		X (*****)		
11. Liu et al.[28]	X (*)	X (**)	X (*)		
12. Mueller et al.[35]	X (*)		X (*/**/***)		X (*)
13. Nikolidakis et al. (2009)	X (*)		X (****)		
14. Polimeni et al.[18]	X (*)		X (*****)		
15. Ramazanoglu et al.[23]	X (*)	X (**)	X (*/**)		
16. Ramazanoglu et al.[24]	X (*)	X (**)	X (*/**)		
17. Schliephake et al.[36]	X (**)		X (*)		X (*/****)
18. Schliephake et al.[9]	X (*/**)		X (*)	X (**)	X (*/****)
19. Schliephake et al.[30]	X (*/**)	X (*)			X (*)
20. Schliephake et al.[22]	X (*)	X (*)			X (*)
21. Schliephake et al.[36]	X (*)			X (**)	X (*)
22. Schliephake et al.[26]	X (*)	X (*/**)			X (*)
23. Schouten et al.[27]	X (**)	X (**)	X (****)		
24. Schulz et al. (2014)	X (*)				X (*/*****)
25. Stadlinger et al. (2009)	X (*)				X (*/****)
26. Stadlinger et al.[12]	X (*)			X (**)	X (*/***)
27. Sverzut et al. (2012)	X (*)				X (*)
28. Wikesjo et al.[10,19,37]	X (***)		X (*)		
29. Wikesjo et al.[10,19,37]	X (***)		X (*****)		
30. Wikesjo et al.[10,19,37]	X (***)		X (*)		

Titanium reference surface (R): *microrough**–sandblasted/acid-etched (20 studies); **polished–machined (4 studies); and ***pure titanium/anodic oxidation (9 studies). Inorganic surface coating (I): *HA, hydroxyapatite (6 studies); **CaP, calcium phosphate (7 studies); and ***bisphosphonate (2 studies). Growth factors surface coating (GF): *rhBMP-2, recombinant human bone morphogenetic protein2 (11 studies); **VEGF-165, vascular endothelial growth factor 165 (3 studies); ***FGF-2, fibroblast growth factor 2 (1 study); ****TGF-β1, transforming growth factor β1 (2 studies); *****rhGDF-5, recombinant human growth differentiation factor 5 (3 studies). Peptide surface coating (P): *bioactive peptide sequence (1 study); **RGD peptide, amino acid sequence: Arg–Gly–Asp (4 studies). Extracellular matrix surface coating (ECM): *collagen type 1 (14 studies); **collagen type 2 (1 study); ***collagen type 3, (1 study); ****chondroitin sulfate (5 studies); and *****hyaluronic acid (1 study).

Results of individual studies

Defect model studies (excluded from the meta-analysis). Six studies analyzed implants in different defect models. For this purpose, periimplant gaps and supraalveolar defects were applied. Especially growth factors were analyzed in supraalveolar defects.De Barros et al.[11] analyzed bone healing around coated implants in a periimplant gap-defect model. The test surface consisted of collagen type 2 and chondroitin sulfate, the control surface of sandblasted/acid-etched titanium. It was concluded that the width of the periimplant gap influences periimplant bone formation, and as a result, lower vertical and horizontal apposition with increasing bone gap sizes was noticed. In proximity to the surface, the collagen/CS coating influenced bone formation positively.

Five studies[15–19] investigated supraalveolar defect models. BMP-2 was used as a coating component in three of these studies.[15,16,19] The reference surface in all cases was anodically oxidized titanium. The test surfaces with a rhBMP-2 surface-coating were on anodically oxidized titanium in all three studies[15,16,19]; the surface in the Wikesjo study was further defined as being a porous oxide. The authors concluded that rhBMP-2 coated anodized implants could stimulate bone formation and increase stability significantly on completely healed alveolar ridges in dogs, while rhBMP-2 on porous oxide implant surfaces induced relevant local bone formation, including vertical augmentation of the alveolar ridge and osseointegration.

Two studies used rhGDF-5 as a coating component[17,18] with test and control surface both being anodically oxidized titanium. Different levels of enhancement in bone formation were described for rhGDF-5.

Non-defect model studies (excluded from the meta-analysis). Five studies analyzed implants in unimpaired bone but were not included in the meta-analysis, as these studies did not perform BIC measurements.

Alghamdi et al.[21] used a test surface with nano-CaP and collagen type 1, and the control surface was pure titanium. They reported that the obtained data failed to provide an effect on bone formation of the collagen coating.

TABLE IV. Studies of the Meta-Analysis

Study	A	GF	P	ECM	Animal Model	Location
1. Barros et al.[29]	HA		Bioactive peptide		Dog	Mandible
2. Germanier et al. (2006)			RGD		Pig	Maxilla
3. Liu et al.[28]	CaP	BMP-2			Pig	Maxilla
4. Mueller et al.[35]		BMP-2/VEGF-126/FGF-2			Pig	Skull
5. Nikolidakis et al. (2009)		TGF-β1			Goat	Femur
6. Ramazanoglu et al.[23]	CaP	BMP-2/VEGF-126			Pig	Skull
7. Schliephake et al.[36]		BMP-2		Collagen 1 + CS	Dog	Mandible
8. Schliephake et al.[9]		BMP-2	RGD	Collagen 1 + CS	Dog	Mandible
9. Schliephake et al.[30]	HA			Collagen 1	Dog	Mandible
10. Schliephake et al.[22]	HA			Collagen 1	Dog	Mandible
11. Schliephake et al.[36]			RGD	Collagen 1	Dog	Mandible
12. Schliephake et al.[26]	HA + CaP			Collagen 1	Dog	Mandible
13. Schouten et al.[27]	CaP	TGF-β1			Goat	Femur
14. Schulz et al. (2014)				Collagen 1 + hualuronic acid	Pig	Maxill
15. Stadlinger et al. (2009)				Collagen 1 + CS	Pig	Mandible
16. Stadlinger et al.[12]			RGD	Collagen 1 + 3	Pig	Mandible
17. Sverzut et al. (2012)				Collagen 1	Dog	Mandible
18. Wikesjo et al.[10,19,37]		BMP-2			Monkey	Maxilla
19. Wikesjo et al.[10,19,37]		BMP-2			Dog	Mandible

Table III shows 19 studies with its surface components, animal models, and implant location.

Ferguson et al.[20] used test surfaces coated with hydroxyapatite, bisphosphonates, collagen type 1/CS, and a sandblasted/acid-etched titanium control surface. The authors concluded that functional surface modifications such as bisphosphonates and collagen coatings seem to enhance early periimplant bone formation. Ferguson et al. used biomechanical and radiographic analyses without histomorphometry.

Hunziker et al.[25] used test surface coated with CaP and BMP-2 and a sandblasted/acid-etched titanium control surface. They concluded that the capacity of BMP-2 to induce local bone formation can be influenced by its mode of delivery.

Langhoff et al.[6] used a test surface containing hydroxyapatite, bisphosphonates, collagen type 1/CS, and a sandblasted/acid-etched titanium control surface. There were no significant differences.

Ramazanoglu et al.[24] used a test surface containing CaP, rhBMP-2, rhVEGF-165, and an acid-etched titanium control surface. It was concluded that a combination of BMP-2 and VEGF has a benefit on bone mineralization and the expression of bone matrix proteins.

Results of Funnel plot. Smaller studies with negative results tend not to be published at all, which seems to be the case in our analysis (Funnel plot). In other words, the studies that were selected and included may represent too positive results.

Synthesis of meta-analysis results

Of the 30 studies of this review, 23 studies measured the BIC. Seven studies did not measure BIC, but other parameters like histomorphometric BV, radiographic parameters, and mechanical removal torque tests were thus excluded from the meta-analysis. The 23 BIC studies contained four defect animal models, which were also excluded. The final meta-analysis was computed with 19 studies as shown in Table IV.

Overall results. For all 19 studies and regardless of surface type, the summary effect size of BIC of the test surface was 3.68 percentage points (pp) higher compared to the reference surface (95% CI −3.86–11.22, $p = 0.339$), which corresponds to a summary relative effect increase of 7.5 pp (Fig. 3). There was a noticeable variation between the studies ($\tau^2 = 244.9$).

Analyzing only studies and data for inorganic surface coatings the mean summary effect size of BIC was 14.71 pp higher compared to the reference surface (95% CI 10.57–18.85, $p < 0.001$), which corresponds to a summary relative effect increase of 43.8 pp. A smaller but still statistically significant difference was found for ECM surface coatings (summary effect size increase of 9.97 pp, 95% CI 4.37–15.56, $p < 0.001$, summary relative effect increase of 21.3 pp). Peptide surface coatings showed a trend toward higher BIC values for test surface compared to reference surfaces (summary effect size increase of 7.13 pp, 95% CI −0.81–15.07, $p = 0.078$, summary relative effect increase of 13.5 pp). No statistically significant difference between test and reference surfaces could be found for growth factor surface coatings (summary effect size decrease of −3.32 pp, 95% CI −16.51–9.86, $p < 0.621$, summary relative effect decrease of −6.8 pp).

The above data included all types of references surfaces. Comparable results were found if only studies with microrough titanium reference surfaces were analyzed. For these

TABLE V. Results of the Meta-Analysis According to Surface Type, Animal Species and Anatomical Locations (*: p-values were deemed significant if <0.05, without correction for multiple testing)

Species/Location	Surface	# Studies	Effect Size	95% CI	Relative Effect (%)	*p* values
	All	13	−0.06	−8.59–8.46	−0.1	0.988
	Inorganic	4	9.3	3.27–15.34	24.2	0.003*
	GF	7	−7.93	−21.16–5.31	−15.7	0.240
	Peptide	4	2.23	−3.82–8.27	3.9	0.471
	ECM	6	7.93	1.07–14.8	15.4	0.024*
Dog	Inoragnic	4	13.68	8.43–18.93	34.2	<0.001*
Dog	GF	3	−8.99	−40.28–22.30	−15.9	0.573
Dog	Peptide	3	10.83	4.30–17.35	24.7	0.001*
Dog	ECM	6	12.64	6.42–18.86	36.2	<0.001*
Pig	Inorganic	2	14.55	5.08–24.02	87.4	0.003*
Pig	GF	3	5.85	0.80–10.90	24.7	0.023*
Pig	Peptide	2	2.31	−9.96–14.59	3.9	0.712
Pig	ECM	4	7.18	−0.92–15.27	13.1	0.082
Goat	GF	2	7.31	−26.40–41.02	14.1	0.671
Maxilla	GF	2	−16.95	−51.80–17.89	−29.7	0.340
Mandible	Inorganic	4	13.68	8.43–18.93	34.2	<0.001*
Mandible	GF	3	−8.99	−40.28–22.30	−15.9	0.573
Mandible	Peptide	4	6.74	−3.02–16.49	12.8	0.176
Mandible	ECM	8	10.36	3.45–17.26	21.3	0.003*
Skull	GF	2	8.08	2.00–14.15	35.8	0.009*
Femur	GF	2	7.31	−26.40–41.02	14.1	0.671

microrough reference surfaces, though the effect size and the relative effect on the BIC were generally smaller, the most pronounced effects were again displayed by inorganic surface coatings, followed by ECM. The effect of peptide coatings was again the smallest, and GF also did not result in a measureable increase in BIC (Table V).

Species. Taking only dog studies into account, significant differences could be found between the BIC of the reference surfaces compared to test surfaces for inorganic surface coatings (summary effect size increase of 13.68 pp, 95% CI 8.43–18.93, summary relative effect increase of 34.2 pp, $p < 0.001$), peptide surface coatings (summary effect size increase: 10.83 pp, 95% CI 4.30–17.35, summary relative effect increase 24.7 pp, $p = 0.001$), and ECM surface coatings (summary effect size increase: 12.64 pp, 95% CI 6.42–18.86, summary relative effect increase of 36.2 pp, $p < 0.001$). No statistically significant difference was observed for dogs with test surfaces with growth factor coatings (summary effect size decrease of −8.99 pp, 95% CI −40.28–22.30, summary relative effect decrease of 15.9 pp, $p = 0.573$).

Conversely, considering only studies using pigs a significant difference in the mean BIC between the reference and the test surface with GF coatings was found (summary effect size increase of 5.85 pp, 95% CI 0.80–10.90, summary relative effect increase of 24.7 pp, $p = 0.023$). The observed difference for peptide coatings was not statistically significant (summary effect size increase of 2.31 pp, 95% CI −9.96–14.59, summary relative effect increase of 3.9 pp, $p = 0.712$), neither was the difference for ECM coatings (summary effect size increase of 7.18 pp, 95% CI −0.92–15.27, summary relative effect increase of 13.1 pp, $p = 0.082$). The results for inorganic surface coatings in pigs were similar to the results in dogs (summary effect size increase of 14.55 pp, 95% CI 5.08–24.02, summary relative effect increase of 87.4 pp, $p = 0.003$). Two goat studies were included into the meta-analyses and showed no statistical significant difference (summary effect size increase of 7.31 pp, 95% CI −26.40–41.02, summary relative effect increase of 14.1 pp, $p = 0.671$). Species specific results are shown in Table V.

Location. The test surfaces using inorganic surface coatings in extraoral locations had a significantly higher BIC compared to the reference surfaces (summary effect size increase of 15.06 pp, 95% CI 6.23–23.89, summary relative effect increase of 68.4 pp, $p = 0.001$). When GF surface coatings were used, no significant effect could be observed (observed difference summary effect size increase of 7.42 pp, 95% CI −6.79–21.62, summary relative effect increase of 18.5 pp, $p = 0.306$). There were not enough studies to compare the peptide and ECM coatings in extraoral locations, as only one study examined ECM surface coatings, and no study examined a peptide surface coating in an extraoral location.

In intraoral locations, test surfaces with inorganic surface coatings (summary effect size increase of 14.54 pp, 95% CI 9.66–19.42, summary relative effect increase of 38.1 pp, $p < 0.001$) and ECM surface coatings (summary effect size increase of 9.96 pp, 95% CI 3.75–16.17, summary relative effect increase of 20.9 pp, $p = 0.002$) had a significantly higher mean BIC compared with reference surfaces. No significant difference could be observed for GF surface coatings (summary effect size decrease of −12.29 pp, 95% CI −32.37–7.79, summary relative effect decrease of 21.7 pp, $p = 0.230$) and for peptide surface coatings (summary effect size increase of 7.13 pp, 95% CI −0.81–15.07, summary relative effect increase of 13.5 pp, $p = 0.078$).

Table V summarizes the results separately for studies performed in different anatomical locations. Studies were only included if at least two studies per group were available. Statistically significant differences were found for test surfaces with inorganic surface coatings and ECM surface coatings compared with reference surfaces in the mandible and between test surfaces with GF surface coatings and reference surfaces for studies in skull bone. Studies using peptide coatings in the mandible showed no significant increase in BIC.

Additional analysis

Results of Kappa measure for intraexaminer agreement GJ and interexaminer agreement GJ–JJ/GJ–BS showed "very good agreement" (Kappa = 1.000). Results of Kappa measure of intraexaminer agreement JJ and interexaminer agreement JJ–GJ/JJ–BS showed "good agreement" (Kappa = 0.732–0.839). Results of the McNemar test between all examiners showed "no evidence for disagreement" (McNemar = 0.250–1.000).

DISCUSSION

Effect of coating

This systematic review and meta-analysis evaluated whether biological implant surface coatings are capable of increasing periimplant bone formation in comparison to uncoated titanium surfaces in large animals. Twenty-four of the 30 studies were published between 2008 and 2013, indicating that this topic is gaining interest. A major finding of this meta-analysis is that biological implant surface coatings in general increase bone formation. The meta-analysis revealed an overall increase of 3.7 pp BIC. Considering the different subgroups of surface coatings, the summary effect size increase was significant for inorganic surfaces (15 pp) and ECM surfaces (10 pp) and showed a statistical trend for peptide surfaces (7 pp). Interestingly, GF coatings showed a mean decrease in BIC of 3 pp.

Inorganic coatings showed the highest increase in BIC in this meta-analysis. The inorganic surface group consisted of CaP coatings (four studies[23,26–28]) and HA coatings (four studies[22,26,29,30]). The results of this group need to be interpreted with caution, as only studies comparing inorganic coatings to organic coatings were included in this review. Studies solely comparing inorganic coatings to uncoated surfaces were not included. For this reason, the data of inorganic coatings are not representative for their general effect and do not allow a general statement on their effect.

Still, the direct comparison of the used inorganic coatings to the organic ones is possible and shows that in this setting only the inorganic coatings and the ECM coatings had a significant effect on the BIC. It is difficult to speculate on the why as the actual processes and interactions that take place during their osseointegration are not completely understood.[31] One reason may be the added structural effects of such coatings, as morphological changes are known to influence cell behavior,[32] and both peptide and GF coatings do not contribute to this aspect. Another possibility is direct and receptor-specific interactions between the coatings and cells. This is possible for both ECM and peptide coatings, with an advantage for ECM coatings as they provide a larger number and greater variation of possible interaction sites. This would agree with the finding of the peptide coatings being slightly better than the GF coatings, as the last generally provide no cell adhesion sites. Neither do inorganic coatings, at least not directly, but inorganic coatings have a large protein binding capacity—larger than a titanium surface, especially one precoated with GF or peptide[9,30]—and may thus very well interact indirectly with cells via binding the respective protein components. Yet, a third possibility is also based on the interaction capacity of the surfaces, in this case with soluble factors like cytokines and growth factors that are secreted during tissue healing. These factors can specifically bind to matrix proteins *in vivo*, which can serve to potentiate their function.[33] If these factors are bound and retained by implant surfaces even for a short time, this may serve to enhance their function and thus the effect of the surface on the surrounding bone. Some organic surface coatings are being designed to specifically exploit this effect, and future studies will show how much this can contribute to bone healing. Currently, the relative contributions of these possible mechanisms are not known, though it may well turn out that no single one dominates in the effect on BIC.

The surprisingly low performance of growth factor coatings may be unexpected as most studies used BMP-2 as a coating protein (seven studies in meta-analysis—Table IV, 11 studies in the entire review—Table II), which is well known to stimulate bone growth even in critical size defects.[34] That no such stimulation of bone growth takes place when BMP-2 is used as a coating may be based on the much smaller amounts that can be immobilized on implant surfaces compared to the carrier-based application in bone defects as BMP amounts of coatings are in the μg range, those of carriers in the mg range. Also, it is possible that GF activity is reduced due to the immobilization process.[9,10,15,16,19,23–25,28,35–37] The same considerations apply to the other growth factors used (Table III), perhaps even to a greater degree as their effects on bone growth can be expected to be generally lower than that of BMP.[38] There was only one exception to the negligible effect of GF on BIC that can be seen if only pig models are considered (see later).

Effect of animal model

A number of different animal models were used in the studies, which implies different dynamics of bone formation especially in early healing intervals.[39] This in turn may have consequences for the observed BIC. For this reason, the difference in BIC was analyzed individually for the most commonly applied animal models (dog and pig).

While inorganic coatings showed a comparable increase of BIC in both models with 14 pp in dogs and 15 pp in pigs, there were differences for the other surfaces studied. In dogs, both ECM coatings (13 pp) and peptide coatings (11 pp) showed a significant increase in BIC; in pigs, ECM coatings only showed a statistical trend (7 pp), while

peptide coatings (2 pp) clearly failed to attain a level of significance. For growth factor coatings, the situation was reversed, as dog studies showed a mean decrease in BIC and pig studies on the other hand showed a significant increase (6 pp).

One reason for the observed differences could be the usually faster bone regeneration in dogs compared to pigs and humans. To highlight different dynamics and levels of bone formation in the two models, the relative BIC increase (summary relative effect) was also calculated and analyzed as it gives a better idea of the degree of the change since it takes the absolute level of BIC into account. A 10 pp increase over a 10–20 pp reference BIC is thus rated differently compared to the same increase over an 80–90 pp reference BIC, so the relative effect takes the influence of the chosen animal model better into account. As an example, ECM coatings showed a mean BIC increase (summary effect size) of 10 pp: 13 pp in dogs and 7 pp in pigs. The summary relative effect of these ECM coatings in comparison to controls, on the other hand, was 21 pp: 36 pp in dogs and 13 pp in pigs. With the exception of GF-coatings, all subgroups showed larger leverage effects in dog studies.

The absolute BIC showed clear differences in the effect of different types of surface coatings depending on the animal model. Even taking animal-based variations into account by calculating the summary relative effect, these differences remain, indicating that they may be based on different responses to different coating types.

Effect of location

Another factor of influence on bone formation is the anatomical location, as bone quality and bone formation dynamics differ between different localizations. For this reason, surface subgroups were also analyzed with regard to the anatomical site. The difference between extraoral and intraoral locations could only be analyzed for inorganic and GF coatings, as there were not enough studies to determine the necessary values for ECM and peptide coatings in extraoral locations. Inorganic coatings showed a significant increase in BIC for both locations of about 15 pp; the summary relative effect increase was twice as high for extraoral locations (68 pp) compared to intraoral ones (38 pp). For GF coatings, BIC increased for extraoral locations (7 pp BIC and 18.5 pp summary relative effect BIC) and decreased for intraoral ones (−12 pp BIC and −21 pp summary relative effect BIC), but both changes were not significant. The BIC values for ECM and peptide coatings in intraoral locations followed the trend observed throughout the study with a significant increase for ECM coatings (10 pp BIC and 20 pp summary relative effect BIC) and a nonsignificant increase for peptide coatings (7 pp BIC and 13 pp summary relative effect BIC), Table IV. Based on the results presented here, there does not seem to be a major effect of location on the BIC, though this is a tentative conclusion as only inorganic coatings and GF coatings could be compared.

Effect of reference surface

It has often been shown that microrough surfaces promote more bone formation in comparison to polished surfaces.[5] As the inclusion criteria of this systematic review were only the presence of an uncoated titanium reference surface, this encompassed polished or machined surfaces as well as any kind of microrough surface. To prevent a false positive result due to the inclusion of smooth surfaces, we separately evaluated those studies that used a microrough titanium reference surface (13 of the 19 studies of the meta-analysis). This analysis supported the overall trend as it also showed a significant increase in BIC only for inorganic and ECM coatings.

LIMITATIONS

The aim of this systematic review was to give an overview on large animal studies investigating the effect of biological implant surface coatings on periimplant bone formation. Furthermore, this review was combined with a meta-analysis for the quantification of the general effect of such coatings on the BIC. The majority of the studies investigated surface coatings with ECM components (especially collagen type I) and growth factors (mostly BMP-2). There are fewer studies applying peptides. The meta-analysis focused on the possible effect of biological implant surfaces coatings on BIC. Most of the biological surface coatings showed significant higher BIC values when compared to controls. The Funnel plot results show that studies, which were selected and included, may represent too positive results. The most common large animal models were dog and pig models. All of the 30 studies used healthy animals, and no systemically impaired animal model was applied. However, some studies applied local defect models. This demonstrates that only few studies analyze implant surface coatings under impaired healing conditions. This is of interest, as in general, there are multiple studies analyzing implants under locally compromised conditions.[40] Since there already is a high clinical implant success rates in unimpaired bone,[41,42] it might be of higher clinical interest to analyze new implant surfaces under more critical circumstances, for example, under the influence of bone augmentation procedures. From a scientific point of view, it needs to be mentioned that this makes the interpretation of the results more complicated as further factors of influence will be introduced in such a study.

Another factor of influence is the mode and time of healing. All studies analyzed unloaded implants, and 29 of the 30 studies used submerged healing. Nevertheless, implant healing time showed large variations ranging from 7 to 168 days. Whereas some studies evaluate a single time point, others evaluated up to three time points. Clinically relevant time points are the first early time points, as this may correlate with possible time points of implant loading. Other influencing factors are implant-related parameters. Effects of implant materials, surface, and design influence bone formation.[43] The single studies show large variations in the number of applied implants. Most studies applied screw-

shaped implants with differences in implant length and diameter. Also, the methods of bone formation analysis differed. Twenty-six of the 30 studies used histology, mostly combined with histomorphometry. Eleven studies used radiographic means, and only four studies used biomechanics. For this reason, the meta-analysis was based purely on BIC measurements. All of these different factors of influence complicate any interstudy comparison.

CONCLUSION

In this systematic review and meta-analysis, we could not find a general statistically significant effect of the biological implant surface coating on periimplant bone growth in large animal models. Taking only studies in consideration, where inorganic or ECM coatings were used, a significant effect could be observed. Whether this positive effect translates to humans and whether this statistical significant effect proves clinical relevance need to be answered in prospective clinical studies.

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DISCLOSURE

No benefit of any kind will be received either directly or indirectly by the authors.

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